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X-RAY DETERMINATION OF CHONDRIOL; A RE-ASSIGNMENT OF STRUCTURE

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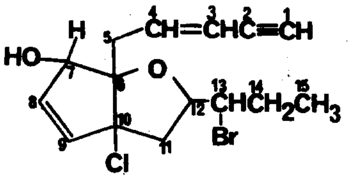
As part of a study of the halogenated antiviral metabolites from the marine alga Chondria oppositiclada Dawson, we had occasion to investigate the ^{13}C nmr spectrum of chondriol. We discovered that chondriol contains a tetrasubstituted double bond (113.3 and 149.8 ppm) not represented in the structure, (1), which was previously proposed for this alcohol.[2] Furthermore, analysis of the 220 MHz proton nmr spectrum of chondriol acetate showed structural features obscured in the 60 MHz spectrum. Specifically, both methylene protons of the pentaenyne group (C-5) were shown to be coupled (J = 8, 4Hz) to a single proton on a carbon (C-6) also bearing an electronegative substituent. In addition, the three-carbon allylic alcohol portion of the molecule showed further coupling. These spectral features cannot arise from the structure 1. Complete spin de-coupling experiments at 220 MHz resulted in the re-assignment of chondriol to structure 2, without assignment of stereochemical features. The nmr data did show the disubstituted double bonds in 2 to be Z (J = 11Hz each).



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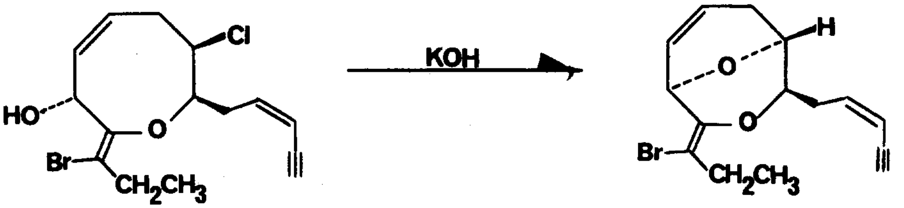

2 3

Treatment of chondriol with warm 5% KOH in methanol gave a smooth conversion to the diether 3, with concurrent loss of hydrogen chloride. Comparison of the nmr spectra of reactant and product confirmed the location of the chlorine atom at C-7 and indicated that the hydroxyl group at C-11 and the chlorine atom at C-7 were of opposite stereochemistry.

In order to further define the stereochemistry of the centers C-6,7,11,12, and 13 in chondriol, crystals of chondriol acetate[2] were subjected to x-ray crystallographic analysis. Crystals of chondriol acetate belong to the monoclinic system, with a = 9.20(3), b = 7.51(5), c = 12.85(6), Å and $\beta = 92.4(7)^{\circ}$. The known optical activity and the systematic extinction on 0k0 (absent if k = 2n+1) uniquely require space group $P2_1$. A calculated density of 1.38 g/cc for z = 2 indicated one molecule of chondriol acetate per asymmetric unit. All data in the hkl and hk$\bar{l}$ octants with $2\theta \leq 42.5^{\circ}$ (985 reflections) were collected on a fully-automated four-circle diffractometer using Zr-filtered MoKα (.7107Å) radiation. During data collection (which took only 8 hours) there was a yellowing of the crystal and a 40% decline in periodically monitored check reflections. After correction for Lorentz polarization, background and decay effects, 807 reflections were judged observed $F_o \geq 2\sigma(F_o)$. The Br position was easily deduced from the Patterson synthesis. A careful choice of a plausible fragment in the resulting Br-phased electron density synthesis, followed by least-squares refinements and subsequent electron density syntheses, revealed all non-hydrogen atoms.[3] Full-matrix least-squares refinements with anisotropic temperature factors for all non-hydrogen atoms converged to an unweighted discrepancy index of 0.075. Anomalous scattering factors were introduced and refinement continued to discrepancy indices of 0.075 and 0.077 for the structure and its mirror image, respectively. All bond distances and angles agree well with generally accepted values, and no abnormally short intermolecular contacts were observed.[4]

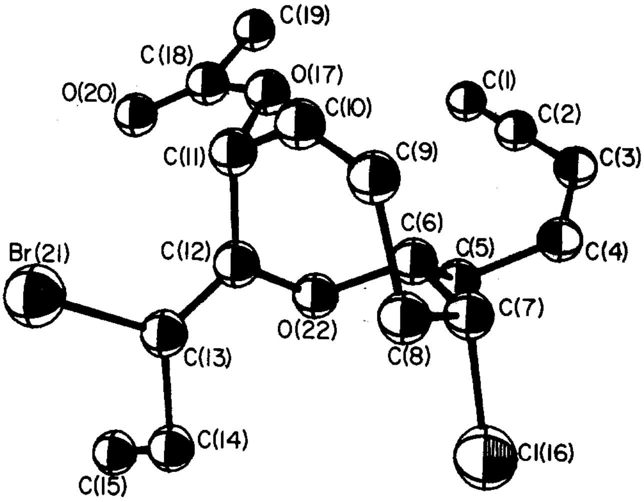

Figure 1, Computer Perspective Drawing of Chondriol Acetate

Mild saponification of chondriol acetate with 5% KOH in methanol regenerated the parent alcohol, 2, and the diether, 3, indicating that no rearrangements had occurred during acetylation. These x-ray results with chondriol acetate (Fig. 1) define chondriol as structure 2 and show the exocyclic double bond at C-12 and

C-13 to be E oriented. One of the protons on C-8 is observed to eclipse the chlorine atom on C-7. The electronic effects of this are noted by the differences in the chemical shifts of these two protons at 3.12 and 2.49δ, respectively.

In comparison to the acetylene-containing compounds from *Laurencia*,[5,6] chondriol differs significantly, since it contains chlorine and has been hydroxylated at carbon-11. In its probable biosynthetic precursor, laurediol,[6] oxidation at C-11 would be a favorable process.

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